REMARKS

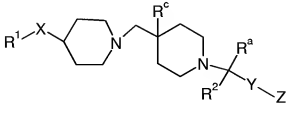
In response to the office action dated January 14, 2008, Applicants have amended claim 1 to promote clarity and remove non-elected subject matter, and withdrawn claims 8 and 12-14, which are directed to non-elected subject matter. Applicants reserve the rights to rejoin the one or more withdrawn claims upon allowance of claim 1. The amendment to claim 1 necessitates cancellation of claim 3. Claims 1, 2, 4-7, and 9 are presented for examination.

Initially, Applicants would like to thank the Examiner for a telephone conference with their counsel on May 9, 2008 to clarify the claim scope under examination. The Examiner indicated that, in view of Applicants' election in the response to restriction requirement filed on December 18, 2007, he examined the entire scope of claim 1 in which X is O and R^1 is phenyl. Further, since the specification states that "[a]ryl includes phenyl or naphthyl," the Examiner indicated that the examination results would be applicable to the claimed compounds in which R^1 is aryl. The Examiner agreed that, to remove non-elected subject matter from claim 1, Applicants are only required to limit claim 1 to compounds in which X is O and R^1 is aryl. Applicants appreciate the Examiner's clarification and have amended claim 1 accordingly.

Rejection under 35 U.S.C. §103(a)

Claims 1-7 and 9 are rejected as being obvious over Lawrence et al. WO 2001/077101 ("Lawrence") in view of Ko et al., WO 2000/35877 ("Ko").

Independent claim 1 is discussed first. Claim 1, as amended, covers compounds of formula (I):

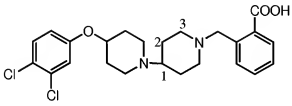
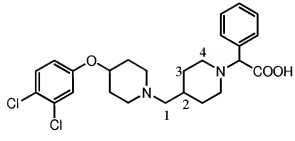


(I)

,

in which X is O; Y is a bond, C_{1-6} alkylene optionally substituted by C_{1-4} alkyl or phenyl, phenylene optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy, or heterocyclylene optionally substituted by halogen, hydroxy, C_{1-4} alkyl or C_{1-4} alkoxy; Z is CO_2R^b, $NHS(O)_2CF_3$, $S(O)_2OH$, $OCH_2CO_2R^b$ or tetrazolyl; R^1 is aryl; R^2 is hydrogen, C_{1-6} alkyl,

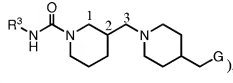
aryl or heterocyclyl; R^a and R^b are, independently, hydrogen or C_{1-4} alkyl; or when R^2 is aryl or heterocyclyl R^a may be C_{2-3} alkylene forming a ring with an ortho position on R^2; and R^c is hydrogen or hydroxyl.

Lawrence describes using bipiperdine compounds for treating a chemokine or H1 mediated disease. *See*, e.g., the abstract. However, Lawrence does not disclose or suggest the compounds of amended claim 1. The Examiner points to the following compound described in Lawrence:  , and states that "it is clear that the prior art differs from the instantly claimed compounds by the presence of a methylene group between the piperidine rings in the [claimed compounds]." *See* the office action, page 4, lines 2-3. Further, the Examiner states that "[t]he elected species of the instant case is shown below … The only difference is a methylene group." *See* the office action, page 4, lines 3-5. Applicants respectfully disagree. The species elected by Applicants is Example 1 described in the present application, i.e.,  . However, Example 1 differs significantly from the compound described in Lawrence relied on by the Examiner. Indeed, Example 1 has a COOH group attached to a non-aromatic carbon atom that is directly connected to the nitrogen atom on the right piperidine ring. By contrast, in the Lawrence compound, the corresponding COOH group is attached to a phenyl group.

Ko does not cure the deficiencies in Lawrence. First, there is no reason for one skilled in the art to combine Lawrence and Ko to provide the compounds of amended claim 1. Ko describes piperidine compounds as modulators of chemokine receptors. *See*, e.g., the abstract. It also describes numerous piperidine compounds containing a methylene groups between two piperidine rings. *See*, e.g., Table 1. However, the compounds described in Ko all have a

functional group Z attached to the available nitrogen atom on one of the two piperidine rings, Z being $C(O)R^3$, $S(O)_2R^3$, $C(O)OR^3$, $C(O)NR^2R^3$, $C(=NR^1)NR^2R^3$, $C(=CHCN)NR^2R^3$, $C(=CHNO_2)NR^2R^3$, $C(=C(CN)_2)NR^2R^3$, or (CR'R')t-phenyl substituted with 0-5 R^{15}. *See*, e.g., claim 1 of Ko. By contrast, the corresponding group in the Lawrence compound relied on by the Examiner is CH_2-phenyl-COOH, in which the group directly connected to a piperidine ring is CH_2, not a functional group as described in the compounds in Ko. Given the significant difference between a function group (e.g., $C(O)NR^2R^3$) and a non-function group (e.g., CH_2), it would not have been obvious to one skilled in the art to extend the teachings in Ko (e.g., compounds having a methylene group between two piperidine rings) to the compounds in Lawrence to provide the compounds of amended claim 1.

Second, even if Lawrence and Ko were combined, the results would not necessarily be the compounds of amended claim 1. Nothing in Lawrence or Ko teaches or suggests to insert a methylene group between two piperidine rings in the Lawrence compound relied on by the Examiner. Indeed, one skilled in the art could have picked the functional group Z in the compounds described in Ko and substituted it for the CH_2-phenyl-COOH group in the Lawrence compound relied on by the Examiner.

In addition, Lawrence only teaches compounds in which the two piperidine rings are arranged in the 4-position relative to each other. As a result, the two nitrogen atoms on the two piperidine rings are spaced apart by precisely three carbon atoms in each direction. *See*, e.g., the chemical formula of the Lawrence compound relied on by the Examiner. Moreover, it is clear from the general formulae on page 138 of Ko that, where the compounds contain two piperidine rings (e.g., ), they are arranged in the 3-position. In other words, the two nitrogen atoms on the two piperidine rings in the Ko compounds are also spaced apart by three carbon atoms. By contrast, as shown above, the compounds of amended claim 1 contain four carbon atoms between the two nitrogen atoms on the two piperidine rings. Thus, even if Lawrence and Ko were combined, the results would be compounds in which the two nitrogen atoms are spaced apart by three carbon atoms, not four carbon atoms as required by the compounds of amended claim 1.

Finally, even if a methylene group were inserted between two piperidine rings in the Lawrence compound, the results would not be the elected species, i.e., Example 1, at least because Example 1 has a COOH group attached to a non-aromatic carbon atom that is directly connected to the nitrogen atom on the right piperidine ring, not to a phenyl group as shown in the structure of the Lawrence compound.

For at least the reasons set forth above, claim 1 is not obvious over Lawrence in view of Ko. Since claims 2, 4-7, and 9 depend from claim 1, they are also not obvious Lawrence in view of Ko.

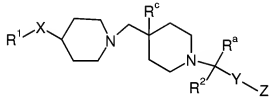
Double patenting rejections

The Examiner rejects claims 1-7 and 9 under the judicially created doctrine of obviousness-type double patenting on four grounds, each of which is traversed below:

I

Claims 1-7 and 9 are provisionally rejected as being obvious over claims 1, 2, 4-7, and 9-11 of copending Application No. 10/508,331 ("the '331 application").

Independent claim 1 is discussed first. It covers compounds of formula (I),

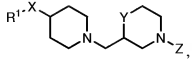


(I)

, which include two 4-piperidine rings connecting to each other via a methylene group.

The Examiner asserts that

> "It is clear that the instant case is drawn to 4-piperidinyl compounds, while the '331 application is drawn towards 3-piperidinyl compounds. Positional isomers, having the same radical on different positions of the molecule, are prima facie obvious, and require no secondary teaching. ... It would be routine for the chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds." See the office action, page 7, lines 1-9.

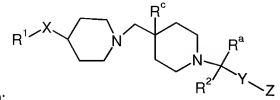
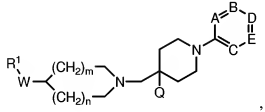
Applicants again disagree. Claims 1, 2, 4-7, and 9-11 of the '331 application cover compounds of the following formula:  , in which Y can CH_2 and Z can be  . These compounds contain a 3-piperidine ring connected to a 4-piperidine ring via a methylene group and are significantly different from those of claim 1 of the present application. The shift in position of the nitrogen atom in one of the two piperidine rings in the compounds of claim 1 of the present application fundamentally alters the orientation of the substituents and therefore alters the shape of the molecules. Such an alteration would lead to significant changes (either beneficial or deleterious) in biological activity of the claimed compounds because their biological activity is highly dependent on their capability of being able to "fit" to specific chemokine receptors. Indeed, the Examiner concedes that "**position isomerism** (emphasis added) has been used as a tool to obtain new and useful drugs." *See* Ex parte Engelhardt cited by the Examiner on page 9, lines 11-12 of the office action. In other words, it is clearly recognized in the art that such a change would not be considered as a simple "optimization" of a biological compound. A skilled chemist seeking to optimize a compound covered by claims 1, 2, 4-7, and 9-11 of the '331 application may consider trying different salts of that compound. However, he or she, in view of the '331 application, would not have made a fundamental structural change to the compound, which would make the compound take an entirely different shape. Indeed, nowhere in the '331 application suggests making such a change.

In sum, it would not have been obvious to one skilled in the art to shift one nitrogen atom in one of the two piperidinyl rings of the compounds of claims 1, 2, 4-7, and 9-11 of the '331 application from 3-position to 4-position to provide the compounds of claim 1 of the present application and expect that the modified compounds would still have similar biological activity.

Thus, claim 1 is not obvious over claims 1, 2, 4-7, and 9-11 of the '331 application. Since claims 2, 4-7 and 9 depend from claim 1, they are also not obvious over claims 1, 2, 4-7, and 9-11 of the '331 application.

II

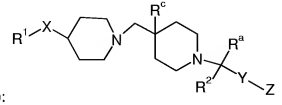
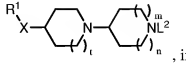
Claims 1-7 and 9 are provisionally rejected as being obvious over claims 1-6 and 8-10 of copending Application No. 10/556,107 ("the '107 application").

Independent claim 1 is discussed first. Claim 1, as amended, covers compounds of formula (I):  (I), which contain at least a methylene group (either substituted or unsubstituted) connecting the group Y-Z to the nitrogen atom on the right piperidine ring. By contrast, claims 1-6 and 8-10 of the '107 application cover compound of the following formula:  , which are significantly different from the compounds of claim 1 of the present application. Specifically, in the compounds of claims 1-6 and 8-10 of the '107 application, an aromatic ring is directly connected to the nitrogen atom on the right piperidine ring, not via a methylene group as required by the compounds of claim 1 of the present application. Such a direct connection leads to electronic interaction between the electron-rich nitrogen atom and the aromatic ring electrons. It would not have been obvious for one skilled in the art to insert a methylene group between the nitrogen atom on the right piperidine ring and the aromatic ring because it would break the electronic interaction mentioned above. Indeed, nothing in the '107 application discloses or suggest such a modification.

Thus, claim 1 is not obvious over claims 1-6 and 8-10 of the '107 application. Since claims 2, 4-7 and 9 depend from claim 1, they are also not obvious over claims 1-6 and 8-10 of the '107 application.

III

Claims 1-7 and 9 are rejected as being obvious over claims 1-4 and 9-18 of U.S. Patent No. 7,179,922 ("the '922 patent").

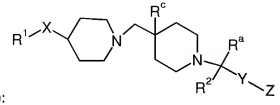
Independent claim 1 is discussed first. Claim 1, as amended, covers compounds of formula (I):  (I), in which Z is CO_2R^b, $NHS(O)_2CF_3$, $S(O)_2OH$, $OCH_2CO_2R^b$ or tetrazolyl. By contrast, claims 1-4 and 9-18 of the '922 patent cover compound of the following formula:  , in which L^2 can be hydrogen, t-butoxycarbonyl, or benzyl. The compounds of claims 1-4 and 9-18 of the '922 patent are significantly different from those of claim 1 of the present application. First, the compounds of claims 1-4 and 9-18 of the '922 patent do not have a methylene group between the two piperidine rings, as required by the compounds of claim 1 of the present application. Introduction of a methylene group would significantly change the relative positions of the key functional piperidine rings. Because the biological activity of a compound is highly dependent on the capability of being able to fit to specific chemokine receptors, such a modification would lead to significant changes in biological activity and may even lead to complete inactivation of the modified compound. Thus, such a modification would not be considered by one skilled in the art as a simple "optimization" of a biological compound. Second, L^2 in the compounds of claims 1-4 and 9-18 of the '922 patent is significantly different from $C(R^aR^2)$-Y-Z in the compounds of claim 1 of the present application. For example, when L^2 is t-butoxycarbonyl, it differs from $C(R^aR^2)$-Y-Z in that the latter group contains at least one methylene group between Z and a piperidine ring. As another example, when L^2 is benzyl, it does not include any of the groups assigned to Z recited in claim 1 of the present application. Given the significant structural differences, it would not have been obvious for one skilled in the art to modify the compounds of claims 1-4 and 9-18 of the '922 patent to provide the compounds of claim 1 of the present application.

Thus, claim 1 is not obvious over claims 1-4 and 9-18 of the '922 patent. Since claims 2, 4-7 and 9 depend from claim 1, they are also not obvious over claims 1-4 and 9-18 of the '922 patent.

IV

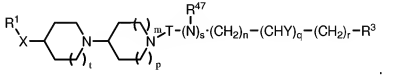
Claims 1-7 and 9 are rejected as being obvious over claims 1-8 and 10-13 of U.S. Patent No. 6,903,115 ("the '115 patent").

Independent claim 1 is discussed first. Claim 1, as amended, covers compounds of formula (I):



(I)

, which contain a methylene group between two piperidine rings. By contrast, claims 1-8 and 10-13 of the '115 patent cover compound of the following formula:



.

The compounds of claims 1-4 and 9-18 of the '922 patent do not have a methylene group between two piperidine rings, as required by the compounds of claim 1 of the present application. As discussed above, because the biological activity of a compound is highly dependent on the capability of being able to fit to specific chemokine receptors, such a modification would lead to significant changes in biological activity and may even lead to complete inactivation of the modified compound. Thus, such a modification would not be considered by one skilled in the art as a simple optimization of a biological compound.

Thus, claim 1 is not obvious over claims 1-4 and 9-18 of the '922 patent. Since claims 2, 4-7 and 9 depend from claim 1, they are also not obvious over claims 1-4 and 9-18 of the '922 patent.

CONCLUSION

Applicants submit that the grounds for rejection asserted by the Examiner have been overcome, and that claims 1, 2, 4-7, and 9 as pending, are now in condition for allowance, an action of which is requested.

The fee in the amount of $120 for the Petition for One-Month Extension of Time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account

authorization. Please apply any other charges to deposit account 06-1050, referencing Attorney's Docket No. 06275-448US1.

Respectfully submitted,

Date: May 12, 2008

/Tony Zhang/
Tony Zhang, Ph.D.
Reg. No. L0256

Fish & Richardson P.C.
Citigroup Center
52nd Floor
153 East 53rd Street
New York, New York 10022-4611
Telephone: (212) 765-5070
Facsimile: (212) 258-2291